



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,987	06/08/2001	Robert M. Townsend	D0009NP/30436.53USU1	1712
23914	7590	09/21/2006	EXAMINER	
LOUIS J. WILLE BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000			GAMBEL, PHILLIP	
			ART UNIT	PAPER NUMBER
			1644	
DATE MAILED: 09/21/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/877,987	Applicant(s) TOWNSEND ET AL.
	Examiner Phillip Gambel	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 11 July 2006.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-36, 38 and 41-44 is/are pending in the application.
4a) Of the above claim(s) 10, 19-36, 41 and 42 is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 1-9, 11-18, 38, 43, 44 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
5) Notice of Informal Patent Application
6) Other: _____

DETAILED ACTION

1. Applicant's amendment, filed 7/11/06, has been entered.

Claims 1, 3, 4, 17 and 18-44 have been amended.

Claims 37 and 39-40 have been canceled previously

Claims 1-36, 38 and 41-44 are pending.

Claims 1-9, 11-18, 38, 43 and 44 are under consideration as they read on the elected invention and species wherein agent one is soluble CTLA4, agent two is anti-CD154 antibody, agent three is anti-LFA-1 antibody and agent four is mycophenolate mofetil as well as the species of cardiac allografts have been acknowledged in the instant application.

Claims 10, 19-36 and 41-42 have been withdrawn from consideration as being drawn to the nonelected inventions / species.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

This Action will be in response to applicant's amendment, filed 7/11/06.

The rejections of record can be found in the previous Office Action, mailed 1/11/06.

3. Upon reconsideration of applicant's amended claims, filed 7/11/06;

the previous rejection under 35 U.S.C. § 112, second paragraph, has been withdrawn.

4. Upon reconsideration of applicant's amended claims, filed 7/11/06;

the previous rejection under 35 U.S.C. § 102(e) as being anticipated by Digan et al. (US 2002/0142000 A1) has been withdrawn.

5. Upon reconsideration of applicant's amendment, filed 7/11/06; the priority date for prior art purposes with respect to Dana et al. (US 2003/0027744 A1) is not the provisional date of 10/22/99 because the PCT was filed prior to 11/29/00.

Therefore, New Grounds of Rejection are set forth herein.

However, it is noted that essentially the same rejection of record under 35 U.S.C. § 103 is set forth herein except for the absence of the previous citation of Dana et al. (US 2003/0027744 A1).

The examiner apologizes for any inconvenience to applicant in this matter.

6. Claims 1-9, 12-18 and 38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320) (1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456), Kenyon et al. (US 2003/0072754), Kirk et al. (US 2002/0119150) and newly added Storb et al. (Blood 94: 2523-2529, 1999) and Heeman et al. (Transplant Immunology 4: 64-67, 1996).

Applicant's arguments, filed 7/11/06, have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments are based upon the reliance of Dana et al. (U.S. 2003/0027744 A1) in the prior art rejection of record.

Dana et al. is no longer applied in the prior art rejection.

The following is reiterated for applicant's convenience.

In contrast to applicant unsupported assertions that Kenyon et al. or Kirk et al. do not teach or provide motivation to combine more than one immunosuppressive agent, the ordinary artisan routinely practiced combining immunosuppressive agents in transplantation therapeutic regimens and which the ordinary artisan would understand from a reasonable reading of the prior art, including paragraphs [0050] – [0051] as well as the Background and paragraph [0007] of the Summary of the Invention of Kenyon et al. as well as paragraph [0057] as well as the Background and paragraphs [0006] and [0009] of the Summary of the Invention of Kirk et al.

Of course, it was noted previously that applicant's assertions were not consistent with the prior art rejection of record nor with conventional immunosuppression provided to transplant patients where the ordinary artisan routinely practiced combination of immunosuppressives to promote long-term graft survival while reducing the toxicity of conventional immunosuppression.

As applicant acknowledged previously, the common goal of the prior art is to provide treatments that are effective with less toxicity than currently available therapeutic agents.

Also, with respect to applicant's amended claims, the following is noted.

Blazar et al. teach that the with first agent which is an inhibitor of costimulatory signal, including CTLA4 and anti-LFA-1 antibody as the second agent which inhibits the generation of a delivery proliferative signal in the T cell (See Summary of the Invention on pages 2-4; Detailed Description of the Invention, including pages 6-8, including Bone

Marrow Transplantation - Inhibition of GVHD on pages 22-23; Tissue and Organ Transplantation on pages 23-24; and Claims).

Kirk et al. clearly teach the synergistic effects both *in vitro* and *in vivo* of combining CTLA4-Ig and anti-CD40L antibodies (e.g. see page 4, column 1; paragraph [0022]).

Larsen et al. also exemplify the advantages of combining anti-CD40L antibodies and CTLA4-Ig in inhibiting immune responses in transplantation regimens (e.g. see Examples).

Newly added Storb et al. teach the advantages of combining different immunosuppressives in prolonging graft survival (see entire document), including improved cardiac and skin xenograft survivals when both CTLA4-Ig and anti-CD40 ligand were combined in blocking both costimulatory signals (see page 2527 , column 2, paragraph 1), combination of mycophenolate mofetil with T cell activation blocker in immunosuppression regimens in transplantation to reduce cytotoxic therapeutic regimens (see entire document, including Abstract and Introduction on page 2523 and Discussion on pages 2526-2528). Therefore, Storb et al. teach combining the particular CTLA4-Ig with anti-CD40 ligand antibody to inhibit both costimulatory signals as well as the contribution of mycophenolate mofetil in prolonging transplant survival and, in turn, the use of these immunosuppressive regimens to reduce cytotoxic regimens in transplantation immunosuppressive regimens.

Heeman et al. teach the use of mycophenolate mofetil in transplantation therapeutic regimens and that this molecule inhibits lymphocyte binding and upregulation of adhesion molecules in allograft rejection (see entire document, including Abstract). It is further noted that mycophenolate mofetil treated individuals have reduced expression of LFA-1 as an important element its the immunosuppressive properties (e.g. see page 66, column 2, paragraph 1).

Given the teachings that LFA-1 was deemed to be an important marker for the activities of mycophenolate mofetil as taught by Heeman et al., the ordinary artisan would have been motivated to include targeting LFA-1 with anti-LFA-1 antibodies in order to increase the efficacy of immunosuppressive regimens, particularly those immunosuppressive regimens that were aimed to reduced cytotoxic elements to the therapeutic regimens associated with transplantation at the time the invention was made.

Therefore, the prior art clearly taught targeting different targets in transplantation regimens, including the particular combinations encompassed by the claimed invention.

Immunosuppression regimens were conventional and standard in transplantation immunosuppressive regimens at the time the invention was made. Therefore, an immunosuppressive such as mycophenolate mofetil was an obvious agent to add to the non-standard/non-conventional immunosuppressives such as CTLA4-Ig, anti-LFA-1 antibody and anti-CD40L antibody. Also, the prior art, including the teachings of Strom et al., is consistent with the motivation and expectation of combining different types of immunosuppressives in order to achieve long term graft survival while diminishing negative side effects of the immunosuppressive regimen at the time the invention was made.

Applicant's arguments have not been found persuasive.

In addition, the following of record is noted.

The prior art provides for the claimed combination of the species of agent one which is soluble CTLA4, the species of agent two which is anti-CD154 antibody and the species of agent 3 which is anti-LFA-1 antibody and mycophenolate mofetil.

For example, Strom et al. teach that the effects of mycophenolate mofetil on purine metabolism are rather selective for activated lymphocytes and, as a consequence, mycophenolate mofetil may replace azathioprine in some drug regimens (see page 454, column 1, paragraph 1, Azathioprine).

Kenyon et al. teach the use of anti-CD40 ligand antibodies in combination with inhibitors of CD80/CD86 interactions with CD28/CTLA4, including CTLA4-Ig, LFA1/ICAM antagonists and mycophenolate mofetil (e.g. see paragraph [0051]) to inhibit transplant rejection (see entire document).

Similarly, Kirk et al. teach the use of anti-CD40 ligand antibodies, particularly in combination with inhibitors of CD80/CD86 interactions with CD28/CTLA4, including CTLA4-Ig (e.g. see paragraphs [0033], [0038] to inhibit transplant rejection.

Therefore, the prior art clearly taught combination therapy for the treatment of graft rejection, including the use of CTLA4-Ig, anti-CD40 ligand antibodies, LFA1/ICAM antagonists and mycophenolate mofetil (MMF).

While applicant has acknowledged that the prior art described each of the agents recited in the claimed methods, applicant argues that there is no evidence showing that the references suggest the claimed invention, particularly the combination of at least three agents previously and now appears to assert the same is true for at least four agents

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case the teachings of the prior art references teach the advantages of combining immunosuppressive agents that target discrete targets to increase the efficacy of immunosuppression and to decrease the toxicity of immunosuppressive regimens. The teachings of the prior art references indicating success in combining immunosuppressive agents to address these known issues and endpoints would have led one of ordinary skill in the art at the time the invention was made to combine the references to solve such well known problems in the art. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144.

In addition, the following of record again is reiterated for applicant's convenience.

Blazar et al. teach methods of inhibiting antigen specific T cell responses, including inhibiting organ graft rejection, including cardiac transplant (see overlapping paragraph on pages 7-8, Tissue and Organ Transplantation on pages 23-24), with first agent which is an inhibitor of costimulatory signal together with a second agent which inhibits the generation of a delivery proliferative signal in the T cell (see entire document, including Detailed Description of the Invention and the Claims). Blazar et al. teach that the with first agent which is an inhibitor of costimulatory signal, including CTLA4 and anti-LFA-1 antibody as the second agent which inhibits the generation of a delivery proliferative signal in the T cell (See Summary of the Invention on pages 2-4; Detailed Description of the Invention, including pages 6-8, including Bone Marrow Transplantation - Inhibition of GVHD on pages 22-23; Tissue and Organ Transplantation on pages 23-24; and Claims). In addition, Blazar et al. teach treating a variety of subjects (page 19, lines 30-32) in a variety of known modes of administration in effects amounts to achieved the desired result (see Compositions on pages 21 and Uses of the Invention on pages 21-24).

Blazar et al. differs from the claimed invention by not disclosing the combination of a third inhibitor of CD40 ligand interactions in methods of inhibiting transplant rejection. It is noted that Blazar et al. does teach targeting gp39 (page 8, line 6), which is the CD40 ligand.

Larsen et al. teach methods of inhibiting immune responses by blocking CD40L/CD40 and CTLA4/CD28/B7 pathways, including inhibiting transplant rejection and cardiac allografts (column 6, paragraphs 4 and 7), including the combination of CTLA4 and anti-CD40 ligand antibody (e.g. MR1) (see Detailed Description of the Invention (e.g. see columns 5-10 and Examples on columns 10-18) (see entire document). Larsen et al. teach the advantages of inhibiting or blocking both CTLA4/B7 and CD40L/CD40 pathways in promoting prolonged immunosuppression (see column 10, paragraph 3 and Discussion on columns 18-19). Larsen et al. teach treating in a variety of subjects (column 8, paragraph 6) in a variety of known modes of administration depending on the location of the tissue or disease being treated as well as the severity and course of the medical disorder in the judgment of the treating physician (see columns 9-10).

In addition to the teachings of Blazar et al. and Larsen et al., it was known at the time the invention was made that the use of immunosuppressive therapy relies upon a number of basic principles as set forth in Strom et al. These principles include that different agents are used, each of which is directed at a different molecular target and aimed at interrupting several discrete stages in the immune activation pathway (e.g. see page 451 and Figure 36.1). Also, additive-synergistic effects are achieved through the application of each agent at a relatively low dose, thereby limiting the toxicity of each individual agents while increasing the total immunosuppressive effect (see page 451, column 1, paragraph 2).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Larsen et al. to those of Blazar et al. to obtain a combining CTLA4Ig and anti-CD40 ligand antibodies, given their increased immunosuppressive properties, to the Blazar's second agent anti-LFA-1 antibodies which inhibits the generation of a delivery proliferative signal in the T cell to increase the efficacy of immunosuppression in therapeutic regimens to promote the long term survival of transplants, including cardiac allografts at the time the invention was made. According to Blazar et al., Larsen et al. and Strom et al., a person of ordinary skill in the art would have been motivated to combine immunosuppressives to produce an increased immunosuppressive regimen in promoting graft survival at the time the invention was made. In addition to the evidence and expectation of success in combining immunosuppressive agents, including those claimed, the use of combination therapy with biologicals would have had the expected advantage of reducing the toxicity of immunosuppressive regimens associated with transplantation at the time the invention was made, as taught by Strom et al.

A person of ordinary skill in the art would have recognized that the combination of three immunosuppressive agents such as CTLA4Ig, anti-CD40 ligand antibodies and anti-LFA-1 antibodies discussed by the references above would have had advantages of increased immunosuppression and decreased toxicity in achieving antigen-specific nonresponsiveness in promoting long terms survival of transplanted tissues and organs at the time the invention was made. Given the referenced and art known modes of administration at the time the invention was made, the ordinary artisan would have administered the agents locally or systemically as well as sequentially or concurrently given the nature of the grafted tissue or organ and the needs of the patient. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Larsen et al. to those of Blazar et al. to obtain a combining CTLA4Ig and anti-CD40 ligand antibodies, given their increased immunosuppressive properties, to the Blazar's second agent anti-LFA-1 antibodies which inhibits the generation of a delivery proliferative signal in the T cell to increase the efficacy of immunosuppression in therapeutic regimens to promote the long term survival of transplants, including cardiac allografts at the time the invention was made. According to Blazar et al., Larsen et al. and Strom et al., a person of ordinary skill in the art would have been motivated to combine immunosuppressives to produce an increased immunosuppressive regimen in promoting graft survival at the time the invention was made. In addition to the evidence and expectation of success in combining immunosuppressive agents, including those claimed, the use of combination therapy with biologicals would have had the expected advantage of reducing the toxicity of immunosuppressive regimens associated with transplantation at the time the invention was made, as taught by Strom et al.

Given the teachings of Kenyon et al. and Kirk et al., the prior art clearly taught combination therapy for the treatment of graft rejection, including the use of CTLA4-Ig, anti-CD40 ligand antibodies, LFA1/ICAM antagonists and mycophenolate mofetil (MMF).

As indicated previously, the prior art clearly taught specific combinations of anti-CD40L antibodies with either antagonists of LFA-1/ICAM or B7/CD28:CTLA4 interactions (e.g. see the teachings of record reiterated above of Larsen et al. and Blazar et al.).

As indicated by the newly added references, Kenyon et al. and Kirk et al. also teach combination therapies employing all of the agents of the claimed methods, including the newly elected mycophenolate mofetil (MMF).

Furthermore, Strom et al. teach the advantages of mycophenolate mofetil in combination therapies for immunosuppression, including immunosuppression of transplant rejection (see above).

A person of ordinary skill in the art would have recognized that the combination of three immunosuppressive agents such as CTLA4Ig, anti-CD40 ligand antibodies, anti-LFA-1 antibodies and mycophenolate mofetil discussed by the references above would have had advantages of increased immunosuppression and decreased toxicity in achieving antigen-specific nonresponsiveness in promoting long terms survival of transplanted tissues and organs at the time the invention was made. Given the referenced and art known modes of administration at the time the invention was made, the ordinary artisan would have administered the agents locally or systemically as well as sequentially or concurrently given the nature of the grafted tissue or organ and the needs of the patient. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

7. Claims 6, 8 and 11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320)(1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456), Kenyon et al. (US 2003/0072754), Kirk et al. (US 2002/0119150), Storb et al. (Blood 94: 2523-2529, 1999) and Heeman et al. (Transplant Immunology 4: 64-67, 1996) as applied to claims 1-9, 12-18 and 38 above

and further in view of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40L antibodies and anti-LFA-1 antibodies, as acknowledged on pages 15-16 of the instant specification and cited in published references) for the reasons of record.

Applicant's arguments, filed 7/11/06, have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments and the examiner's rebuttal are addressed above.

Art Unit: 1644

Again, Dana et al. (U.S. 2003/0027744 A1) is no longer applied in the prior art rejection.

Applicant's arguments, filed 7/11/06, have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same as addressed above, particularly with respect to over Blazar et al. (WO 95/34320)(1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456).

Applicant's arguments have not been found persuasive.

8. Upon reconsideration of applicant's amended claims and the duplicative nature of the prior art 103 rejections, the previous rejection under 35 U.S.C. § 103(a) as being unpatentable over Digan et al. (US 2002/0142000 A1) (see entire document, including claims, particular claim 28) in view of Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456) and of the known availability of the deposited material producing the known immunosuppressives selected from the group consisting of CTLA4, anti-CD40L antibodies and anti-LFA-1 antibodies, as acknowledged on pages 15-16 of the instant specification and cited in published references) has been withdrawn in the interest of simplifying the prior art rejections.

9. Claims 6 and 43-44 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Blazar et al. (WO 95/34320) (1449; Exhibit 86) in view of Larsen et al. (U.S. Patent No. 5,916,560) (1449; Exhibit 230), Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456), Kenyon et al. (US 2003/0072754), Kirk et al. (US 2002/0119150), Storb et al. (Blood 94: 2523-2529, 1999) and Heeman et al. (Transplant Immunology 4: 64-67, 1996). as applied to claims 1-9, 12-18 and 38 above and further in view of Peach et al. (US 2003/0219863).

Applicant's arguments, filed 7/11/06, have been fully considered but are not found convincing for the reasons of record.

Applicant's arguments and the examiner's rebuttal are addressed above.

The teachings of Blazar et al. in view of Larsen et al., Strom et al., Kenyon et al. and Kirk et al. are provide above and differ from the claimed methods by not disclosing the L104EA29YIg CTLA4 molecule.

Art Unit: 1644

Peach et al. teach the use of L104EA29YIg in treating immune system diseases in order to regulate T cell interactions as well as its use with other immunosuppressives, (see entire document, including paragraphs [0067] – [0069]). Peach et al. also teach that the L104EA29YIg binds with higher avidity than CTLA4 (e.g. see Summary of the Invention and Examples).

One of ordinary skill in the art would have been motivated to substitute the L104EA29YIg for CTLA4Ig in the combination therapy taught by of Blazar et al. in view of Larsen et al., Strom et al., Kenyon et al. and Kirk et al. (see above), given its higher binding avidity taught by Peach et al. Therefore, a person of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Phillip Gambel, Ph.D., J.D.
Primary Examiner
Technology Center 1600
September 18, 2006